General

Guideline Title

Boceprevir for the treatment of genotype 1 chronic hepatitis C.

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Boceprevir for the treatment of genotype 1 chronic hepatitis C. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Apr. 50 p. (Technology appraisal guidance; no. 253).

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Boceprevir in combination with peginterferon alfa and ribavirin is recommended as an option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease:

- Who are previously untreated or
- In whom previous treatment has failed

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Genotype 1 chronic hepatitis C

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Infectious Diseases

Internal Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of boceprevir for the treatment of genotype 1 chronic hepatitis C

Target Population

Treatment naïve or treatment experienced adults with genotype 1 chronic hepatitis C with compensated liver disease

Interventions and Practices Considered

Boceprevir in combination with peginterferon alfa and ribavirin

Major Outcomes Considered

- Clinical effectiveness
  - Sustained virologic response (SVR)
  - SVR achievement by response at treatment weeks 4 and 8
  - End of treatment response rates
  - Relapse rates
  - Adverse effects of treatment
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by Southampton Health Technology Assessments Centre (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of Manufacturer's Approach to Systematic Review

Description of Manufacturer's Search Strategy

The manufacturer's literature searches were checked by an information scientist. Overall, the search strategies were considered sound, containing just a few minor inconsistencies. Evidence Review Group (ERG) adaptation of the strategies produced no further useful results. The databases and hosts used, dates of execution, and search strategies were all clearly recorded in the manufacturer's submission (MS). Acceptable search filters were employed. Searches were re-run by the ERG on the Cochrane database producing identical results. Due to differing host systems between those employed in the MS and by the ERG, searches on Medline and EMBASE were not directly comparable with variation in search syntax giving slight differences in return of numbers. It is noted that all searches were limited to English Language. Searches re-run by the ERG on National Health Service Economic Evaluation Database (NHS EED) were comparable. The ERG searched the following trials registries: controlled-trials.com, UK Clinical Research Network (UKCRN) Portfolio and ICTRP (World Health Organisation [WHO] International Clinical Trials Registry Platform). The US Food and Drug Administration (FDA) and European Medicines Agency (EMEA) websites were also checked for further information. The results were checked by an ERG reviewer. No additional trials identified were relevant to the decision problem.

Statement of the Inclusion/Exclusion Criteria Used in the Study Selection

The MS clearly states the inclusion and exclusion criteria, and these reflect the final scope issued by NICE and the licensed indication. Quality of the randomised controlled trials (RCTs) was not stated as an inclusion or exclusion criterion. Setting was not stated in the final scope and was not used as an inclusion criterion.

A flow diagram showing the number of studies from the database searches that were included and excluded at each stage of the review is presented in the MS. The diagram does not include publications identified through manual searches of conference proceedings from two conferences; numbers included and excluded from these searches are detailed separately, and sufficient information is given about these. Reasons for excluding studies at the full publication review stage are provided, along with the number excluded for each reason.

Studies had to be randomised controlled trials to meet the inclusion criteria. The manufacturer does not explicitly consider issues of bias or study quality at the stages of study searching, screening and selection. A critical appraisal of the included RCTs, however, is presented in the MS.

Identified Studies

The MS identified five RCTs (four from the database searches and one from the manual searches), shown in Table 1 of the ERG report (see the 'Availability of Companion Documents' field). All of the studies were sponsored by the manufacturer. Two RCTs were of treatment naïve patients (one was a phase II and one was a phase III trial). Three RCTs were of treatment experienced patients (one was a phase II trial and two were phase III trials). All the identified RCTs meet the inclusion criteria for the review, and the MS appears to have included all relevant RCTs. The ERG searches did not identify any further relevant studies.

Economic Evaluation

Critical Appraisal of the Manufacturer's Submitted Economic Evaluation

Manufacturer's Review of Published Economic Evaluations

A systematic search of the literature was conducted by the manufacturer to identify economic evaluations of pharmacological treatments of chronic hepatitis C virus (HCV) genotype 1 infection. The inclusion criteria state that cost-effectiveness studies (including cost-utility analyses) of pegylated

or non-pegylated interferon α-2a or α-2b monotherapy or in combination with ribavirin, boceprevir, or telaprevir in adult patients with genotype 1 HCV would be included. The exclusion criteria state that studies set in a non-European context, reported only as conference abstracts, posters or abstracts, or assessing HCV patients co-infected with human immunodeficiency virus (HIV), hepatitis B, substance dependent or illegal drug users were excluded. Forty three studies were included for full review. However, none of the published economic evaluations identified compared boceprevir to alternative pharmacological treatments for the treatment of chronic HCV genotype 1 infection.

See Section 4.2 of the ERG report (see the "Availability of Companion Documents" field) for more information.

Number of Source Documents

Clinical Effectiveness

- Five randomised controlled trials (RCTs) and 2 ongoing trials were identified, and 3 RCTs were included in the review in full.

Cost-Effectiveness

- No published studies met the criteria for inclusion.
- The manufacturer presented an economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by Southampton Health Technology Assessments Centre (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Description and Critique of the Approach to Validity Assessment

The manufacturer's submission (MS) provides a quality assessment of the identified randomised controlled trials (RCTs) and a summary of the quality assessment for each RCT is tabulated. The manufacturer's quality assessment follows the NICE criteria and is appropriate. Table 2 of the Evidence Review Group (ERG) report (see the "Availability of Companion Documents" field) shows the assessment of study quality for each RCT by the manufacturer and ERG. As this table shows, the ERG agrees partly with the MS assessment of study quality.

Description and Critique of the Manufacturer's Approach to the Evidence Synthesis

The tabulated data in the clinical effectiveness review reflect the data in the trials except for a few minor incorrect values, but these do not change the interpretation of the data. The narrative review reflects the data in the trials, with a few exceptions (see the ERG report [see the "Availability of

Companion Documents" field] for details).

An overall problem with the narrative review is that much of the interpretation is based on comparison of percentage values between groups without reference to odds ratios (ORs), relative risks (RRs) (for adverse events [AE]), confidence intervals or significance tests.

A meta-analysis is provided that includes two of the studies. The meta-analysis examines the proportion of patients with cirrhosis or who were null-responders who achieved sustained virologic response (SVR). The included trials appear to be comparable.

A fixed effects model was used in the meta-analysis, but the MS does not give a justification for this choice. The MS also does not report relative or absolute differences. No summary measure of the treatment effect is given and the results seem to be simple averages by treatment group (clarification was requested from industry). Confidence intervals are provided for this. The MS does not provide any other statistics. Sensitivity analyses were not conducted.

See Section 3 of the ERG report (see the "Availability of Companion Documents" field) for additional information.

Economic Evaluation

The ERG have considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 8 of the ERG report (see the "Availability of Companion Documents" field), drawn from common checklists for economic evaluation methods.

The economic evaluation uses a Markov model to estimate the cost-effectiveness of boceprevir/pegylated interferon/ribavirin (BOC/PEG/R) compared with PEG/R in adult chronic hepatitis C virus (HCV) genotype 1 patients with compensated liver disease, either treatment naïve or treatment experienced. The model adopted a lifetime horizon to capture lifetime costs and health outcomes, with a yearly cycle length after the initial 72 weeks, during which treatment and follow-up are modelled using a weekly cycle. In the economic model, patients are distributed across different degrees of fibrosis (F0-F4) and then may progress to more severe stages of liver disease. After successful treatment, patients achieve SVR, which is considered a cure for F0-F3 (non-cirrhotic) patients.

Results are presented for lifetime costs and quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) for a cohort representing the total UK HCV population.

The manufacturer deterministic sensitivity analysis showed that the base case ICER was most sensitive to the efficacy estimates (probability of achieving SVR), health state utilities, costs, and the discount rates. The probabilistic sensitivity analysis estimates there is a 92.5% and 100% probability of BOC/PEG/R being cost-effective, relative to PEG/R alone.

See Section 4 of the ERG report (see the "Availability of Companion Documents" field) for more information on cost-effectiveness methods.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a

document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

The manufacturer of boceprevir submitted a de novo economic analysis that assessed the cost-effectiveness of boceprevir plus peginterferon alfa and ribavirin for the treatment of genotype 1 chronic hepatitis C in adults who were previously untreated or who had experienced treatment failure. Data from the clinical trials were used to inform model inputs for treatment effects and adverse reactions. The model simulates treatment and the subsequent natural history of chronic hepatitis C virus (HCV), depending on whether the patient experiences a sustained virological response. The model has a total of 16 health states according to disease stage and treatment response. The natural progression of the disease was modelled using disease-specific transition probabilities between health states.

The manufacturer presented base-case analyses for boceprevir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin in treatment-naive and previously treated patients. The manufacturer's results show that adding boceprevir to peginterferon alfa and ribavirin increased the cost of treatment but was associated with more quality-adjusted life years (QALYs) than treatment with peginterferon and ribavirin alone.

The Evidence Review Group (ERG) conducted an exploratory analysis using parameter values from National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance 200 for progression rates between fibrosis states for mild to moderate HCV. The ERG found that these changes significantly increased the incremental cost-effectiveness ratio (ICERs) for both treatment-naive patients and previously treated patients. However, the ERG indicated that the transition probabilities used by the manufacturer were appropriate because they were from a more recent source. The ERG ran an additional analysis that explored the impact of having no anaemic patients receiving erythropoietin and simultaneously increasing the discontinuation rate for medical reasons (including anaemia). It confirmed that this had little impact on the ICER.

Summary of the Appraisal Committee's Key Conclusions

The Committee considered the manufacturer's economic model and its associated assumptions, and the critique and exploratory analyses conducted by the ERG, and noted the manufacturer's model was similar to that used in NICE technology appraisal guidance 200. The Committee concluded that the model closely adhered to the NICE reference case for economic analysis and was acceptable for assessing the cost-effectiveness of boceprevir.

The Committee concluded that the base-case ICERs for boceprevir plus peginterferon alfa and ribavirin compared with peginterferon alfa and ribavirin alone for the treatment-naive population (£11,601 per QALY gained) and the previously treated population (£2909 per QALY gained) were robust to sensitivity analyses and were all below £20,000 per QALY gained, demonstrating that boceprevir represents a cost-effective use of National Health Service (NHS) resources for patients with genotype 1 chronic hepatitis C.

See Sections 3 and 4 of the original guideline document for details of the economic analysis provided by the manufacturer, the Evidence Review

Group comments, and the Appraisal Committee considerations.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated for each recommendation.

The Appraisal Committee considered clinical and cost-effectiveness evidence and a review of this submission by the Evidence Review Group. For clinical effectiveness, three randomised controlled trials were the main source of evidence. For cost-effectiveness, the manufacturer's model was considered.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of boceprevir for the treatment of genotype 1 chronic hepatitis C

Potential Harms

The summary of product characteristics lists the following adverse reactions for boceprevir as the most frequently reported: fatigue, anaemia, nausea, headache and dysgeusia.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Contraindications

Contraindications

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Clinical Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the National Health Service (NHS) in England and Wales on implementing National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on the NICE website (http://guidance.nice.org.uk/TA253)
    - Costing template and report to estimate the national and local savings and costs associated with implementation
    - Audit support for monitoring local practice

Implementation Tools

Audit Criteria/Indicators

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Boceprevir for the treatment of genotype 1 chronic hepatitis C. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Apr. 50 p. (Technology appraisal guidance; no. 253).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Apr

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Professor Peter Clark (*Chair*), Consultant Medical Oncologist, Clatterbridge Centre for Oncology; Professor Jonathan Michaels (*Vice Chair*), Professor of Clinical Decision Science, University of Sheffield; Professor Darren Ashcroft, Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester; Dr Matthew Bradley, Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline; Dr Ian Campbell, Honorary Consultant Physician, Llandough Hospital; Dr Ian Davidson, Lecturer in Rehabilitation, University of Manchester; Professor Simon Dixon, Professor of Health Economics, University of Sheffield; Dr Martin Duerden, Assistant Medical Director, Betsi Cadwaladr University Health Board; Dr Alexander Dyker, Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle, Gillian Ells, Prescribing Advisor, NHS Sussex Downs and Weald; Dr Jon Fear, Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds; Paula Ghaneh, Senior Lecturer and Honorary Consultant, University of Liverpool; Dr Susan Griffin, Research Fellow, Centre for Health Economics, University of York; Professor John Hutton, Professor of Health Economics, University of York; Professor Peter Jones, Emeritus Professor of Statistics, Keele University; Dr Steven Julious, Senior Lecturer in Medical Statistics, University of Sheffield; Dr Vincent Kirkbride, Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield; Rachel Lewis, Advanced Nurse Practitioner, Manchester Business School; Professor Paul Little, Professor of Primary Care Research, University of Southampton; Professor Femi Oyebode, Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health; Dr John Radford, Director of Public Health, Rotherham Primary Care Trust; Dr Phillip Rutledge, GP and Consultant in Medicines Management, NHS Lothian; Dr Brian Shine, Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford; Dr Murray D Smith, Associate Professor in Social Research in Medicines and Health, University of Nottingham; Paddy Storrie, Lay Member; Dr Lok Yap, Consultant in Acute Medicine and Clinical Pharmacology, Whittington Hospitals NHS Trust

Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Boceprevir and telaprevir for the treatment of genotype 1 chronic hepatitis C. Costing template. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012. (Technology appraisal guidance; no. 253). Electronic copies: Available from the National Institute for Health and Clinical Excellence (NICE) Web site .
- Boceprevir for the treatment of genotype 1 chronic hepatitis C. Clinical audit tool. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012. (Technology appraisal guidance; no. 253). Electronic copies: Available from the NICE Web site .
- Boceprevir for the treatment of genotype 1 chronic hepatitis C. Evidence review group report. Southampton (UK): Southampton Health Technology Assessments Centre; 2011 Oct 4. 50 p. Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site .

Patient Resources

The following is available:

- Boceprevir for genotype 1 chronic hepatitis C. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Apr. 5 p. (Technology appraisal guidance; no. 253). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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